Remarks

Claims 1-13 are pending in the subject application and are now presented to the Examiner for further review. Favorable consideration of these claims, in view of the remarks set forth herein, is earnestly solicited.

Claims 1-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ninomiya *et a.* (U.S. Patent No. 4,695,568) in view of McInally *et al.* (PCT/SE98/00641 English equivalent U.S. Patent No. 6,303,613) and Kelley *et al.* (U.S. Patent No. 5,708,033). The applicants respectfully traverse this ground for rejection because the cited references, taken either alone or in combination, do not disclose or suggest the applicants' unique and advantageous use of 4-2(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine (MCI-225) or a salt thereof to treat pain, functional bowel disorder, or fibromyalgia.

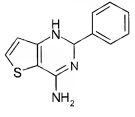
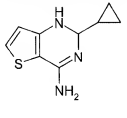
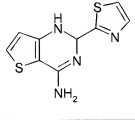
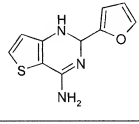
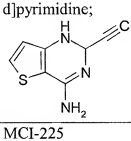
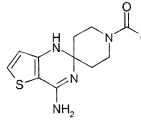
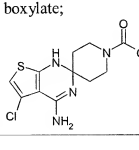
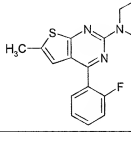
The Ninomiya *et al.* reference teaches that 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride (MCI-225) is potentially useful for the treatment of depression. As acknowledged at page 3 of the outstanding Office Action, "Ninomiya *et al.* fails to teach the treatment of pain, irritable bowel syndrome, and fibromyalgia."

McInally *et al.* disclose a vast array of compounds that are said to be useful for the treatment of a range of conditions that include osteoarthritis, rheumatoid arthritis, rheumatoid sponydlitis, gouty arthritis and other arthritic conditions, inflamed joints, pain, acute or persistent inflammatory or neuropathic pain or pain of a central origin (nociceptive or neuropathic), and conditions of the gastrointestinal tract such as irritable bowel syndrome (column 8, line 23-25, 38, and 40-45). McInally *et al.* do not disclose or suggest MCI-225.

There are literally millions of compounds that fall within the broad disclosure of the McInally *et al.* reference. Certainly it cannot reasonably be stated that McInally *et al.* teach the use of each and every one of these millions of compounds for the treatment of pain as claimed by the current applicant. In assessing what the skilled artisan could glean from the teachings of McInally *et al.* it is most helpful to consider the compounds that McInally *et al.* set forth as the preferred compounds. These compounds are set forth in, for example, claim 5 of the McInally *et al.* patent.

In comparing MCI-225 with the compounds disclosed by McInally et al, it is apparent that there is significant structural dissimilarity. This dissimilarity is described in detail below. Furthermore, the biological activity decribed for the McInally *et al.* compounds is not even within the known biology of MCI-225. Specifically, the activity of the McInally *et al.* compounds as nitric oxide synthase inhibitors (see column 8 lines 10-25) has not been shown for MCI-225.

Regarding the preferred compounds as specified in Claim 5 of the McInally *et al.* reference, the following structures help to illustrate the important structural differences between the McInally *et al.* compounds and the compound (MCI-225) used in the applicants' claimed method:

7-amino-4,5-dihydro-5-phenylthieno[3,2-d]pyrimidine; 	5-cyclopropyl-4,5-dihydro-7-aminothieno[3,2-d]pyrimidine; 	5-ethyl-4,5-dihydro-7-aminothieno[3,2-d]pyrimidine; 
5-(2-thiazolyl)-4,5-dihydro-7-aminothieno[3,2-d]pyrimidine; 	5-(2-furyl)-4,5-dihydro-7-aminothieno[3,2-d]pyrimidine; 	7-amino-4,5-dihydro-5-ethynylthieno[3,2-d]pyrimidine; 
ethyl 7'-aminospiro[piperidine-4,5'(4'H)-thieno[3,2-d]pyrimidine]-1-carboxylate; 	ethyl 4-amino-3'-chlorospiro[piperidine-4,6'(7'H)-thieno[2,3-d]pyrimidine]-1-carboxylate; 	MCI-225 

From a comparison of these structures it can be seen that the McInally *et al.* compounds all have a partially unsaturated 6-membered ring containing 2 nitrogens, whereas MCI-225 has a fully saturated ring. Furthermore, the carbon between the two nitrogens in the pyrimidine ring has a tetrahedral 3-dimensional geometry whereas the analogous carbon in MCI-225 is tri-substituted and in the same plane as its substituents. Additionally, the McInally *et al.* compounds have a hydrophilic amino group in the bottom of the 6-membered ring (this can act as a hydrogen bond donor). None of the exemplified McInally *et al.* compounds possess the lipophilic 2-fluorophenyl group of MCI-225 at the bottom of the 6-membered ring (which cannot act as a hydrogen bond donor). In contrast, MCI-225 possesses a basic nitrogen on the pendant piperazine ring, which is not possessed by the McInally *et al.* preferred compounds. This basic nitrogen can behave as a hydrogen bond acceptor, and influences overall physical properties such as pKa and solubility.

These structural differences give rise to important differences in the biological activity of MCI-225 compared to the McInally *et al.* compounds. Specifically, the critical feature of all the McInally *et al.* compounds is the ability to inhibit nitric oxide synthase; this is not even a component of MCI-225's known activity. Rather, the useful therapeutic activity of MC-225 is attributed to noradrenaline uptake inhibition, serotonin 5-HT3 antagonism and serotonin uptake inhibition.

The Kelley *et al.* reference does not cure or even address the shortcomings of the primary Ninomiya *et al.* and McInally *et al.* references as discussed in detail above.

The mere fact that the purported prior art could have been modified or applied in a manner to yield the applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). As the CAFC has established, an invention will not be rendered obvious merely by combining teachings found in the prior art. *ACS Hospital Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). There must be some suggestion or incentive in the prior art to make the combination. *Id.* Also, the prior art must suggest that this combination would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In view of the unpredictability in the art, the applicants' claim to the use of a specific, structurally dissimilar compound cannot be fairly stated to be obvious. Therefore, the results of applicants' empirical research are not rendered obvious by the cited references. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103 based on Ninomiya in view of McInally *et al.* and Kelly *et al.*

Claims 5-11 have been provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-7 of copending Application No. 10/519,594. Upon an indication of allowability of the claims in the current case, the applicants will either cancel or amend the claims in the '594 application.

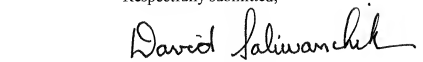
Claims 12 and 13 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30, 31 and 35 of copending Application No. 10/525,532. Upon an indication of the allowability of claims 12 and 13 in the current application, the applicants will entertain filing a Terminal Disclaimer with respect to the '532 application.

In view of the foregoing remarks and the amendment above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to the undersigned's Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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